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Your reference PHGB020033

28 MAR 2002

Patent application number
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P01/7700 0.00-0207295.7

Full name, address and postcode of the or of each applicant (*underline all surnames*)

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THE NETHERLANDS

Patents ADP Number (*if you know it*) 7419294001

If the applicant is a corporate body, give the country/state of its incorporation THE NETHERLANDS

Title of the invention AN INFORMATION SERVER WITH A DATABASE OF INFORMATION ABOUT PARTICULAR LOCATIONS AND A TELEPHONE FOR REMOTELY ACCESSING AND QUERYING THE SAME

Name of your agent (*if you have one*)
"Address for service" in the United Kingdom to which all correspondence should be sent (*including the postcode*)

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Patents ADP number (*if you know it*) 8226961001

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DESCRIPTION

AN INFORMATION SERVER WITH A DATABASE OF INFORMATION ABOUT PARTICULAR LOCATIONS AND A TELEPHONE FOR REMOTELY ACCESSING AND QUERYING THE SAME.

The invention relates to an information server with a database of information about particular locations, a telephone for remotely accessing and querying the database and a related sign.

In the United Kingdom, the government organisation Ordnance Survey has a website at url http://www.ordnancesurvey.gov.uk which discloses the use what it refers to as Topographic Identifiers (TOIDs) which are 16 digit numbers which label map features such as points, lines and areas. The stated purpose of these TOIDs is to provide a consistent, flexible and interchangeable mapping format whereby, for example, map features can be viewed by classification.

US patent 4577062 (Hilleary et al.) discloses a method of dispensing particular information automatically from a changing data source to a user whereby the user accesses the information by dialling the dissemination service using telephone equipment. The caller's call and subsequent dialled digital sequences, corresponding by prearrangement to specific information requests, are automatically processed. The information from a data base is transmitted to the caller by audible synthesised speech signal through the caller's telephone.

US patent 6225944 (Hayes) discloses a method of manual reporting of location data in a mobile communications network. In particular, at lines 25 to 30 of column 2 disclose where "the method gathers location information from a Global Positioning System (GPS) receiver and then converts the location information into a Teletype/Telephony Device for the Deaf (TTY/TDD) format before transmitting the location information". As disclosed at lines 23 to 25 of column 5, this may be done using transmission protocols including Baudot,

V21, DTMF (Dual Tone Multi-Frequency), and EDT (European Deaf Telephony), and the V.18 protocol".

In accordance with the present invention, a server and corresponding telephone are provided wherein the server containing a database of records with each record being identified by a location tag and containing information about a particular location; and wherein at least some of the location tags are neither descriptive of the name of organisations which conducts business at the corresponding particular locations nor form part of the address of those locations. Using the corresponding communications telephone, a user may remotely access and query the database using the telephone keypad to enter a location tag to retrieve information about a particular location contained in a record identified by that location tag.

As access is with a telephone keypad, it is convenient if each location tag consists only of numbers 0 to 9 and, optionally, star (*) and hash (#) symbols.

Information about a particular location is intended to include, for example, co-ordinates of that location (i.e. latitude, longitude etc.), the address of that location, directions to that location and the identity of organisations which conducts business at that particular location.

Also provided in accordance with the present invention is a sign located and conveying a location tag of the aforementioned type and, in particular, in the form of a wall plaque appended to a building wherein information contained in a record identified by that location tag relates to an organisation which conducts business in that building.

Where information about a particular location is retrieved from the server and contains either the co-ordinates of that location, the address of that location or directions to that location, the telephone may be configured to provide to the user directions to that location from the present location of the telephone. Where this is the case, it is convenient if the telephone comprises position determining means to whereby it is able to determine its own location,

for example such as a GPS receiver, telephone network positioning circuitry and the like.

The inventor has realised that it is may be desirable for a mobile user carrying a mobile telephone to access information about particular locations on the move, and in particular about buildings and the organisations located therein. For example, the application of an arbitrary, numerical location tag on a sign appended to a building provides an immediate reference with which a user may query a database using a telephone

The present invention will now be described, by way of example only, with reference to the accompanying schematic drawings in which:

Figure 1 shows mobile cellular telephones MS1 and MS2 communicating via a nearby cellular telephone network base station BS and a public switched telephone network (PSTN) with a remote, Internet based information server (IS) in accordance with the present invention;

Figure 2 shows the mobile cellular telephone MS1 of figure 1 in greater detail;

Figure 3 shows the mobile cellular telephone MS2 of figure 1 in greater detail;

Figure 4 shows the remote, Internet based information server (IS) of figure 1 in greater detail; and

Figure 5 shows a wall plaque in accordance with the present invention.

Figure 1 shows mobile cellular telephones MS1 and MS2 in possession of respective users (not shown) and registered with nearby cellular telephone network base station BS facilitating voice and data communication with that base station and corresponding cellular telephone network. Data communication is intended to include sending text messages (for example using the short message service (SMS) protocol) and accessing the Internet (for example using WAP or i-mode protocols). In particular, mobile telephones MS1 and MS2 are communicating via the base station and a public switched

telephone network PSTN with a remote, Internet based information server IS in a manner according to the present invention.

In figure 2, telephone MS1 is shown in greater detail comprising a communications transmitter (Tx) and receiver (Rx) 20 connected to a communications antenna 21 and controlled by a communications microprocessor (μp) 22 for communication with the base station BS with which it is registered. Figures 3 shows telephone MS2 in greater detail configured similarly to telephone MS1 except that telephone MS2 further comprises a GPS receiver (GPS Rx) 30 connected to a GPS antenna 31. Also, the communications microprocessor (μp) 22 is further configured to acquire and track GPS signals for the purpose of deriving pseudorange information from which the location of the mobile telephone can be determined using conventional navigation algorithms. Such methods for GPS signal acquisition, tracking and position determination are well known, for example, GPS Principles and Applications (Editor, Kaplan) ISBN 0-89006-793-7 Artech House. Also, the design and manufacture of telephones of the type of telephones MS1 and MS2 are well known and those parts which do not directly relate to the present invention will not be elaborated upon here further.

Figure 4 shows the remote, Internet based information server IS in greater detail. As illustrated, the server is arranged to receive, and deliver, signals to the Internet and includes a transmitter (Tx) and receiver (Rx) 40 for receiving queries from mobile telephones MS1 and MS2. The server further includes a database 42 under control of a microprocessor (μp) 41 wherein the database's records containing information about respective places which are indexed by a location tag, the format of which is a number which may optionally be interspersed with the symbols # and * which can be found on the keypads of telephones MS1 and MS2.

Information about a particular location is obtained in accordance with the present invention as illustrated in the following examples:

Example 1

Suppose that a user in possession of telephone MS1 has received a text message from a friend with whom the user is intending to meet and wherein the text message states that the friend is at "012#345*678" which refers to a location tag on a plaque as shown in figure 5 which is hung on a wall of the entrance to a restaurant in which restaurant the friend is waiting to meet the user.

At the time when the location tag was created and the plaque first placed at the restaurant, a record was created in the database held on the information server IS, the record including the name and address of the restaurant, and generic directions to the restaurant wherein the entry was tagged by the location tag "012#345*678".

The user of telephone MS1 connects to the Internet using their mobile cellular telephone in a conventional manner by transmitting and receiving data from the telephone MS1 via the base station BS, a cellular network system controller (SC) and a public switched telephone network PSTN. The user then accesses the information server (IS) via the Internet and queries the database held on the information server by sending the location tag "012#345*678" to the information server. The information server (IS) replies sending the name and address of the restaurant, and generic directions to the restaurant, i.e. the contents of the record created when the location tag was created. In addition, the information server provides an url to a mapping website which if selected, would display a map of the area in which the restaurant is located.

Thus, upon querying the database, the information server replies with said details which enables the user of telephone MS1 to find the restaurant in order to meet the user's friend.

Example 2

As example 1 except that a user using telephone MS2 may access the information server IS and send to the information server the user's current position obtained using the GPS receiver of telephone MS2 in addition to the location tag "012#345*678". The information server replies sending specific directions from the user's current position to the restaurant.

At the time of writing, the mapping website http://www.multimap.co.uk enables an url to be created which if selected directs a user to a map of a predefined area. Similarly, the same website will also provide directions from one location to another and accordingly, the mechanisms for this functionality are not described here in detail.

As an alternative to a GPS receiver in example 2 above, other forms of positioning technology may be used including telephone network positioning such as E-OTD and other GPS type solutions such as GLONASS and GALILEO.

From reading the present disclosure, other modifications will be apparent to persons skilled in the art. Such modifications may involve other features which are already known in the design and use of computer systems and component parts thereof and which may be used instead of or in addition to features already described herein. Although claims have been formulated in this application to particular combinations of features, it should be understood that the scope of the disclosure of the present application also includes any novel feature or any novel combination of features disclosed herein either explicitly or implicitly or any generalisation of one or more of those features which would be obvious to persons skilled in the art, whether or not it relates to the same invention as presently claimed in any claim and whether or not it mitigates any or all of the same technical problems as does the present invention. The applicants hereby give notice that new claims may be formulated to such features and/or combinations of such features during the prosecution of the present application or of any further application derived therefrom.

CLAIMS

1. An information server containing a database of records wherein each record is identified by a location tag and contains information about a particular location; wherein at least some of the location tags are neither descriptive of the name of organisations which conducts business at the corresponding particular locations nor form part of the address of those locations; and wherein a user may remotely access and query the database using a telephone keypad to enter a location tag to retrieve information about a particular location contained in a record identified by that location tag.

2. A server according to claim 1 wherein each location tag consists only of numbers 0 to 9 and star (*) and hash (#) symbols.

3. A server according to claim 2 wherein each location tag consists only of numbers 0 to 9.

4. A server according to any preceding claim wherein at least one record contains the co-ordinates of a particular location.

5 . A server according to any preceding claim wherein at least one record contains the address of a particular location.

6. A server according to any preceding claim wherein at least one record contains directions to a particular location.

7. A server according to any preceding claim wherein at least one record contains information about an organisation which conducts business at a particular location.

8. A telephone adapted to connect to an information server containing a database of records wherein each record is identified by a location tag and contains information about a particular location; wherein at least some of the location tags are neither descriptive of the name of organisations which conducts business at the corresponding particular locations nor form part of the address of those locations; and wherein a user may remotely access and query the database using the telephones keypad to enter a location tag to retrieve information about a particular location contained in a record identified by that location tag.

9. A telephone according to claim 8 wherein the database can be queried by a user entering or having previously entered a location tag on the telephone's keypad using only numbers 0 to 9 and star (*) and hash (#) symbols.

10. A telephone according to claim 9 wherein the database can be queried by a user entering or having previously entered a location tag on the telephone's keypad using only numbers 0 to 9.

11. A telephone according to any of claims 8 to 10 wherein the information about a particular location retrieved from the server contains either the co-ordinates of that particular location, the address of that particular location or directions to that particular location; and wherein the telephone is configured to provide to the user directions to that particular location from the telephone's present location.

12. A telephone according to claim 11 wherein the telephone comprises position determining means to determine its present location.

13. A sign located at a particular location and conveying a location tag which identifies a particular record in a database containing information about that location, wherein the location tag is one of many such location tags held in the data base, at least some of which are neither descriptive of the name of an organisation which conducts business at that location nor forms part of the address of that location.

14. A sign according to claim 13 wherein the location tag it conveys is neither descriptive of the name of an organisation which conducts business at that location nor forms part of the address of that location.

15. A sign according to claim 13 or claim 14 wherein the location tag consists exclusively of numbers 0 to 9, star (*) and hash (#) symbols.

16. A sign according to claim 15 wherein the location tag consists exclusively of numbers 0 to 9.

17. A sign according to any of claims 13 to 16 in the form of a wall plaque appended to a building wherein information contained in a record in the database identified by that location tag relates to an organisation which conducts business in that building.

ABSTRACT

AN INFORMATION SERVER WITH A DATABASE OF INFORMATION ABOUT PARTICULAR LOCATIONS AND A TELEPHONE FOR REMOTELY ACCESSING AND QUERYING THE SAME.

An information server and corresponding telephone are disclosed wherein the server containing a database of records with each record being identified by a location tag and containing information about a particular location; and wherein at least some of the location tags are neither descriptive of the name of organisations which conduct business at the corresponding particular locations nor form part of the address of those locations. Using the corresponding communications telephone, a user may remotely access and query the database using the telephone keypad to enter a location tag to retrieve information about a particular location contained in a record identified by that location tag.

Also disclosed is a sign located at a particular location and conveying a location tag of the aforementioned type and, in particular, in the form of a wall plaque appended to a building wherein information contained in a record identified by that location tag relates to an organisation which conducts business in that building.

[figure 1]

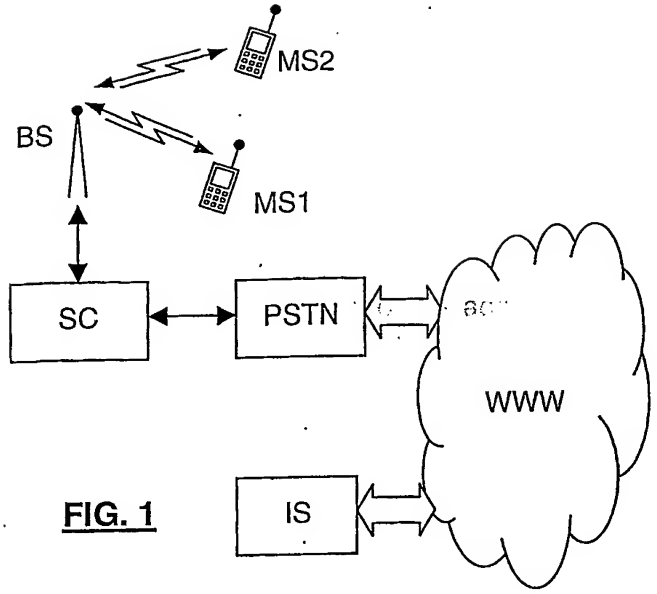


FIG. 1

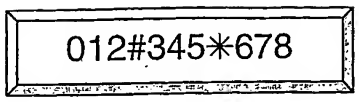


FIG. 5

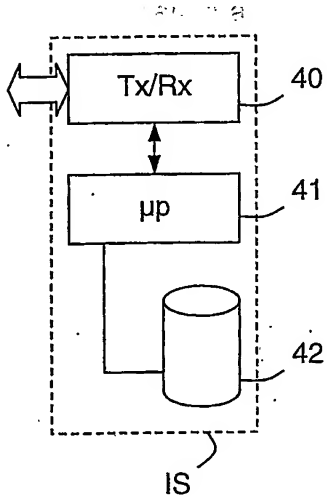


FIG. 4

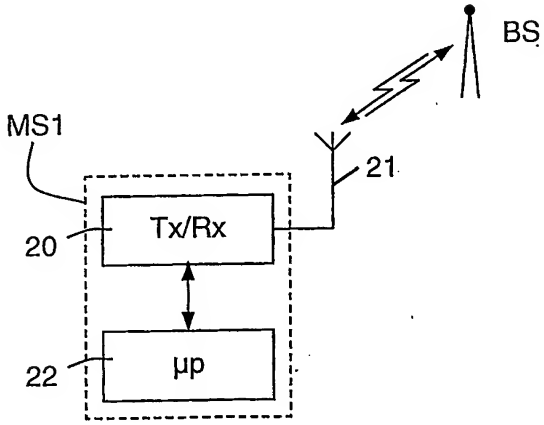


FIG. 2

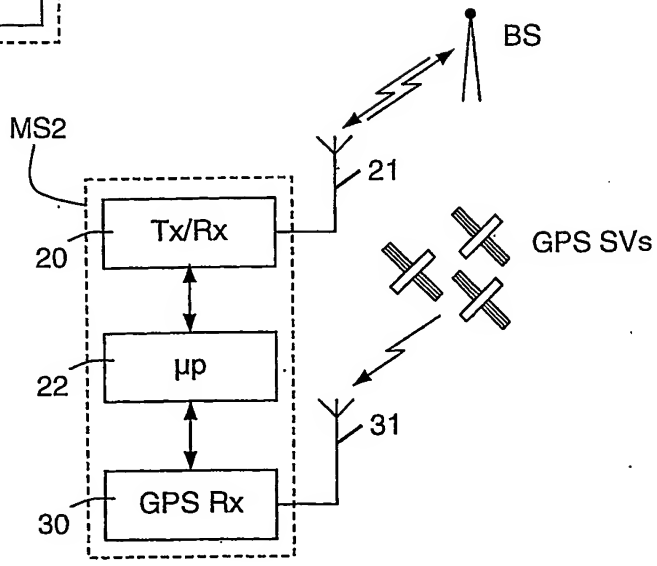


FIG. 3

alum and formulation excipients, including urea, in rabbits. On Day 1, twelve rabbits received three 0.5 ml intramuscular injections to the paravertebral muscle of the test and control articles as follows:

Group	N	Site 1	Site 2	Site 3
1	6 males	HP3	HP3 placebo	Saline
2	6 males	HP3, but with 7.5mg/dose urea	HP3 alum control	Saline

Clinical signs, body weights, dermal irritation, hematology, coagulation, and serum chemistry were evaluated. Three animals per group were necropsied on days 3 and 15. A macroscopic postmortem examination was conducted and injection sites, stomach, duodenum and macroscopic lesions were examined for histopathology.

There were no deaths or treatment-related effects on body weight, hematology, coagulation, or serum chemistry. Very slight erythema was seen in two animals given HP3 (Group 2, site 1). Well-defined erythema was seen in one animal given the alum control (Group 2, site 2), which diminished and was resolved completely by Day 5. There were no dermal observations in any other animals. Apparent bruising at the test sites correlated with erythema in two animals.

Injection site histopathology in animals necropsied on day 3 consisted of acute inflammation/focal necrosis attributed to needle trauma. In animals euthanized on day 15, the injection site lesions consisted of small focal clusters or accumulations of macrophages. These were typical sequelae following acute inflammation and focal necrosis seen two weeks prior. No differences in the size or character of the inflammatory components between groups or injection sites could be detected on histologic examination.

Conclusion: Under the conditions of the study, *H. pylori* antigens (HP3) adjuvanted with alum and containing low (3.75 mg/dose) or high (7.5 mg/dose) urea were well tolerated when administered to rabbits as a single intramuscular injection. Findings in skin (erythema) and muscle (bruising/inflammation/necrosis) were comparable across groups and sites. Local reactogenicity of formulations with or without HP3 antigens was of a low order of magnitude and was similar to either alum in saline or the HP3 placebo formulation (no antigens).

Tolerance study

A tolerance study (code 7795) was performed in beagle dogs infected with *H.pylori*.

Dogs were infected with *H.pylori* using three oral administrations (10^9 cfu each) administered every other day [117]. Following infection, 2 animals/sex/group were given intramuscular injections of either CagA+VacA+NAP (10μg or 50μg of each antigen per dose) or the alum control. A fourth group was treated with a conventional regimen including antibiotics and a proton pump inhibitor (clarithromycin 250mg, metronidazole 250mg, bismuth citrate 60mg, omeprazole 20mg). Serological

and endoscopic evaluations were performed 7, 11, 17, and 27 weeks following the first administration:

Group	Number of Animals		Treatment	Route of Administr'n	Treatment Days
	Males	Females			
1	2	2	1.0 mg alum	Intramuscular	1, 8, 15
2	2	2	50 µg each antigen	Intramuscular	1, 8, 15
3	2	2	10 µg each antigen	Intramuscular	1, 8, 15
4	2	2	Antibiotics + PPI	b.i.d. oral	daily 1–15

Animals in groups 2 and 3 exhibited an antibody response against each of the three antigens. A dose-response was most pronounced for the NAP component (Figure 4). Vaccination with either antigen dose did not cause any adverse effects in terms of clinical signs, body weight, injection site reactions, body temperature, hematology, or serum chemistry as compared to the control group.

Evaluation of gastric biopsies by rapid urea test at 7 and 11 weeks post-vaccination revealed persistent *H. pylori* infection in all animals given adjuvant or antigen. In animals given conventional antibiotic treatment, 1/4 and 2/4 were positive for infection at weeks 7 and 11, respectively. Evaluation of gastric biopsies by immunohistochemistry using an anti-VacA-specific monoclonal antibody confirmed infection in all control animals at both timepoints. In treated groups immunohistochemistry results were variable, with 2 or 3 animals in each group scored as negative. Results are summarised in Figure 5.

At 17 weeks, *H. pylori* infection was detected by rapid urease test in 4/4 in group 1, 2/4 in group 2, 2/4 in group 3, and 2/4 in group 4. In contrast to the week 7 and 11 assessments, the immunohistochemical studies confirmed the rapid urea test results.

Conclusion: The results of these studies suggest that a mixture of VacA, CagA and NAP given intramuscularly induces partial eradication of *H. pylori* infection and has a beneficial effect on the histological severity of post-infection gastritis. In addition, there was no evidence that the enhanced immune response elicited by the antigens was associated with any gastrontestinal or systemic adverse effects.

GLP safety and tolerance study (single dose)

A single dose safety and tolerability study (code UBAW-154) was performed in rabbits. The objective of this study was to evaluate the safety and tolerability of a single dose of HP3 administered intramuscularly to NZW rabbits. A secondary immunogenicity assessment was also included as a study parameter. The study consisted of three groups of 4/sex/group. Each animal either received an alum/saline mixture (Group 1), an alum/HP3 placebo formulation (Group 2), or the HP3 (Group 3). A single intramuscular dose (0.5 mL) was injected into the left quadriceps muscle on day 1 of the study. Two animals/sex/group were euthanised for a comprehensive macroscopic necropsy and tissue collection on days 3 and 15.

Group	Treatment	Day 3 Necropsy	Day 15 Necropsy
1	Alum control	2/sex	2/sex
2	HP3 Placebo	2/sex	2/sex
3	HP3	2/sex	2/sex

Potential toxicity was evaluated based on clinical and injection site observations, body weights, physical examinations (body temperature, respiratory rate, heart rate, and capillary refill time) ophthalmic examinations, food consumption, clinical pathology (hematology, coagulation, and serum chemistry parameters), terminal organ weights, and macroscopic & microscopic evaluation of selected tissues. Serum was collected from all animals for analysis of antibody titres to HP3.

There were no deaths, no treatment-related adverse effects on any antemortem study parameters, and no relevant changes in terminal organ weights. The only dermal observation was for male number 5 (Group 2) which had a "very slight" erythema score at 24 hours post-dose that resolved by the 48-hour observation. Macroscopic postmortem findings at the injection site consisted of purple discoloration in 1/2 Group 1 females and 1/2 Group 3 males. With the exception of injection sites, there were no microscopic alterations that could be attributed to treatment. Any abnormalities noted (minor inflammatory or degenerative changes) were of the type/incidence/severity considered to be background in this strain and age of rabbit [118]. Microscopic injection site findings were minimal-to-mild and noted as follows:

Group Number		1 (Alum)				2 (HP3 Placebo)				3 (HP3)			
Finding	Day	3		15		3		15		3		15	
	Number M/F	2	2	2	2	2	2	2	2	2	2	2	2
Per-acute hemorrhage		0	0	1	0	0	0	0	0	0	0	0	0
Granulomatous inflammation		1	1	0	0	0	0	0	0	0	0	0	0
Acute inflammation		0	0	0	0	0	0	0	0	1	0	0	0
Interstitial hemorrhage		1	1	0		0		0		1		0	

Based on the similarities in the histopathology regardless of treatment, the single intramuscular injection of HP3 was well tolerated by male and female rabbits. Any observations on day 3 were gone by day 15, indicating recovery or reversibility.

Analysis of day 15 serum samples for anti-NAP, CagA, and VacA antibodies indicated that low but measurable levels of IgG to all three antigens were found in all four group 3 rabbits (see above). Control rabbits were negative for antibodies.

Conclusion: Under the conditions of the study, a single 0.5 ml intramuscular injection of HP3 was well tolerated and immunogenic in male and female NZW rabbits. The local reactogenicity of HP3 was of a low order of magnitude and was similar to either the alum control or the placebo.

GLP safety and tolerance study (multiple dose)

A single dose safety and tolerability study (code UBAW-155) was performed in rabbits. The objective of this study was to evaluate the safety and tolerability of multiple (6) doses of HP3, once per week for six weeks by intramuscular injection to NZW rabbits. A secondary immunogenicity assessment was also included as a study parameter. The study consisted of three groups of 6/sex/group. Each animal either received the alum control, the placebo, or HP3. The dose volume was 0.5 mL alternately injected into the right and left quadriceps muscles on days 1, 8, 15, 22, 29, and 36 of the study. Three animals/sex/group were euthanised for a comprehensive macroscopic necropsy and tissue collection on days 38 and 50:

Group	Treatment*	Number		Day 38 Necropsy		Day 50 Necropsy	
		M	F	M	F	M	F
1	Alum/Saline	6	6	3	3	3	3
2	Alum/HP3 Placebo	6	6	3	3	3	3
3	HP3 Vaccine	6	6	3	3	3	3

Potential toxicity was evaluated based on the following parameters: daily clinical signs, dermal injection site observations (24 and 48 hours post-dose for each dose), body weights, physical examinations (body temperature, respiratory rate, heart rate, and capillary refill time), ophthalmic examinations, food consumption, clinical pathology (hematology, coagulation, and serum chemistry parameters), terminal organ weights, full macroscopic postmortem examination, and microscopic evaluation of selected tissues:

Bone marrow	Injection site	Spleen
Eyes with optic nerve	Kidneys	Thymus
Femorotibial joint	Liver	Urinary bladder
Femur	Lung	Lesions
Heart	Lymph nodes	

Observations of "very slight" dermal erythema at 24 hours post-dose were sporadic and resolved by the 48-hour observation. There were no apparent differences in the incidence or severity of dermal observations between the three groups.

There were no deaths and no treatment-related adverse effects on any antemortem study parameters (including body temperatures). There were some statistically-significant differences between groups in a few hematology, serum chemistry and coagulation parameters, however, all values were within the range of normal for this age and strain of rabbit, the changes were of small magnitude, and there was no consistent relationship to duration of dosing.

Macroscopic postmortem findings at the injection site consisted of discoloration (red/purple/tan) of the quadriceps in a few group 1 and 3 males and females. These sites of discoloration corresponded to several histologic findings, which are summarized in the following table:

Group Number		1 (Alum)				2 (HP3 Placebo)				3 (HP3)			
Finding	Day	38		50		38		50		38		50	
	Number M/F	3	3	3	3	3	3	3	3	3	3	3	3
Spleen													
-Follicular hyperplasia		0	0	1	1	1	1	0	1	3	3	3	3
Grade 1		0	0	1	1	1	1	0	1	1	1	3	2
Grade 2		0	0	0	0	0	0	0	0	2	2	0	1
Injection site, Right		0		0		0		0		0		0	
Per-acute hemorrhage			1		0		0		0		2		1
Myofiber lysis			1		0		0		0		2		0
-Eosinophil infiltration			0		0		0		0		0		0
Injection site, Left													
-Chronic inflammation		1	0	0	1	0	0	0	0	1	1	0	0
-Interstitial hemorrhage		1	0	0	0	0	0	0	0	0	1	0	0
-Per-acute hemorrhage		0	0	0	0	0	0	0	0	0	0	1	1
-Myofiber lysis		0	0	1	0	0	0	0	0	0	0	1	1
-Eosinophil infiltration		0	0	0	1	0	0	0	0	0	1	0	0
-Proteinaceous debris		0	0	1	0	0	0	0	0	0	0	0	0
-Granulomatous inflammation		0	0	0	0	0	0	1	0	0	0	0	0

Two animals, one in group 1 and one in group 3, had a whitish discoloration at the injection sites noted at necropsy, but there were no correlating microscopic lesions.

Microscopic examination of the injection sites revealed that any inflammation seen in the alum controls (group 1) and HP3 placebo controls (group 2) was comparable to the HP3 vaccine injection sites. Mild granulomatous inflammation was noted in one male in group 2. The macrophage cytoplasm was distended with a granular amphophilic material, putatively alum. Granulomatous inflammation associated with i.m. administration of aluminium-based adjuvants has been reported in several species [119,120].

HP3-related microscopic alterations were noted in the spleen of all group 3 animals at both days 38 and 50. Follicular hyperplasia (B-cell dependent peri-arteriolar regions) occurred with increased incidence and severity when compared to groups 1 or 2. A slight increase in the average severity of lymphoid hyperplasia was noted for both sexes on day 38 compared to day 50. Such findings may be related to the immunological response of the rabbits to the HP3 vaccine.

With the exception of injection sites and spleen, there were no microscopic alterations that could be attributed to treatment. Any other abnormalities noted were of the type/severity/incidence considered to be background in this strain and age of rabbit [118].

Serum was collected from all animals for analysis of antibody titres to HP3. All 12 rabbits immunised with HP3 had detectable antibody titres to each of the three antigens by day 15. IgG antibody titres in all group 3 rabbits were higher on day 29 and were sustained at the same level on days 38 and 50 (See above). All control rabbits gave negative results.

Conclusion: Under the conditions of the study, administration of six 0.5ml intramuscular injections of HP3 on a once-per-week schedule was well tolerated and immunogenic in male and female NZW rabbits. The local reactogenicity of HP3 was of a low order of magnitude and was similar to either alum in saline or the placebo formulation.

Human administration

A typical human immunisation will use three intramuscular injections of up to 25µg each of NAP, CagA, and VacA antigens with alum adjuvant. The animal toxicology studies utilised a high human dose of HP3 in rabbits weighing up to approximately 4 kg. An adult body weight of 60 kg can be used as a conservative estimate. Therefore, on a body weight basis, each dose given to these rabbits would be at least 15 times higher than in a human adult. Also, the triple human regimen was exceeded by an additional three doses in the multiple-dose rabbit study.

Based on these toxicity and immunogenicity results, it can thus be expected that an immunotherapeutic (once per week for three weeks) or a prophylactic (once per month for three months) clinical regimen of intramuscular injections of 10µg/dose or 25 µg/dose of CagA. VacA and NAP will be immunogenic and well tolerated in humans. Any local effects should be comparable to those seen with alum adjuvant and systemic effects should be consistent with other intramuscular administrations of protein antigens adjuvanted with alum.

For human use, a typical vaccine is a sterile preparation of purified CagA, VacA and NAP, adjuvanted with aluminium hydroxide, in an isotonic buffer solution for intramuscular injection. The *H.pylori* antigens are expressed in genetically-engineered *E.coli* cells, utilising plasmid vector expression systems. Because of the relative insolubility of the VacA antigen, the vaccine will include urea in the amount of 2.9-4.1 mg/dose. The vaccine is provided in a pre-mixed format in syringes containing the antigens and the adjuvant. These syringes should be stored refrigerated between 2-8°C until ready for administration. The vaccine should be shaken before use. The vaccination site should be disinfected with a skin disinfectant (*e.g.* 70% alcohol). Before vaccination, the skin must be dry again. The content of pre-mixed single-dose vaccine in the syringe (0.5 ml) is applied intramuscularly into alternating sides of the upper arm (M. deltoideus). using a 1 to 1½ inch needle.

Two alternative vaccine compositions for human use have the following components in a single 0.5 ml dose and have a pH in the range 6.5 to 7.5:

Component	Amount per final dose	
	Low dose	High dose
$Al(OH)_3$	0.5 mg	0.5 mg
NAP	10 µg	25 µg
CagA	10 µg	25 µg
VacA	10 µg	25 µg
Sodium phosphate ($NaH_2PO_4.H_2O$)	10 mM (0.69 mg)	10 mM (0.69 mg)
Sodium chloride (NaCl)	2.13 – 2.77 mg	2.13 – 2.77 mg
Urea	2.9 – 4.1 mg	2.9 – 4.1 mg
H_2O	Up to 0.5 mL	Up to 0.5 mL

Trace amounts of chloramphenicol may also be present.

Human testing — safety and immunogenicity

These two compositions (and a placebo in which antigens were omitted) were tested in humans in a randomised, controlled, single-blind, dose-ranging, and schedule-optimising study with the aim of evaluating safety and immunogenicity in healthy adults. Two test populations were used: one negative for *H.pylori* infection (57 patients) and the other positive for *H.pylori* infection (56 patients). Compositions were administered as 0.5ml doses from pre-filled syringes.

The 57 HP–negative volunteers were split into seven groups to receive the high (H; 25µg of each antigen) or low (L; 10µg of each antigen) dose vaccine, or the placebo (P; no antigen) with two different administration schedules. The first dose was given at time zero. In groups 1 to 5, three subsequent doses were given at 1, 2 and 4 months ('monthly' groups). In groups 6 & 7, two subsequent doses were given at 1 and 2 weeks ('weekly' groups):

Group	*n*	First dose	Second dose	Third dose	Fourth dose
1	7	L	L	L	P
2	7	H	H	H	P
3	7	L	L	P	L
4	8	H	H	P	H
5	9	P	P	P	P
6	9	L	L	L	—
7	10	H	H	H	—

Demographic data for the 57 volunteers were as follows:

Parameter		Monthly doses (*n* = 38)	Weekly doses (*n* = 19)	All patients (*n* = 57)
Age	mean (years)	29.9	28.9	29.6
	standard dev^n	6.3	5.7	6.1
	range	20-40	20-40	20-40
Sex	(% male)	53	37	47
Ethnicity		100% caucasian	100% caucasian	100% caucasian

Safety

The following safety parameters were monitored:

- Local and systemic reactions (up to day 6 post-injection).
- Adverse and serious events (for entire study period).
- Standard lab parameters *i.e.* serum chemistries and renal function (Na, K, Cl, HCO_3, urea, creatinine), complete blood count (WBC and differential, Hb, haematocrit, platelets), liver function (ALT, AST, alkaline phosphatase, bilirubin, prothrombin time, total protein, albumin).

Data on erythema, induration, malaise, myalgia, headache, arthralgia, fatigue and fever are shown, in that order, in Figures 6 to 13. Figures 6 & 7 show local reactions, whereas figures 8 to 13 show systemic reactions. Short-lasting pain was reported by around 89% of non-placebo subjects,

compared to 78% of placebo subjects. Pain was predominantly mild and resolved after injection. Systemic reactogenicity results are summarised in the following table:

Adverse event (frequency ≥ 5%)	Monthly ($n = 29$)	Weekly ($n = 19$)	Placebo ($n = 9$)
Any adverse event	14	15	7
Administration site reactions and general disorders	8	11	5
Gastrointestinal symptoms	3	3	2
Infections	3	3	0
Musculo-skeletal symptoms	2	0	0
Nervous system disturbances*	2	6	0
Skin and subcutaneous tissue manifestations	2	0	1

* headache, dizziness, akinesia, disturbances of alertness

The frequency and severity of local and systemic reactions were as expected in this population. Adverse events were mild in nature, transitory (lasting from a few hours up to an average two days), and were well in agreement with previous observations during clinical studies with aluminium hydroxide as an adjuvant. No serious adverse events related to the administration of the composition occurred in the volunteers. Local reactions were not frequent, except for local pain at the injection site in all groups. Induration and erythema occurred more often in the 'weekly' groups. The most frequently reported solicited systemic reactions among all groups, of any severity, were fatigue, headache and malaise. Local and systemic post-immunisation reactions were usually mild and resolved within 24-72 hours. Administration of the composition does not significantly alter laboratory parameters. Compositions of the invention are therefore safe for human administration.

Immunogenicity

The following immunogenicity parameters were monitored:

- Serum IgG specific for CagA, VacA and NAP.
- Proliferative responses driven by CagA, VacA and NAP.

Immune responses are shown in Figure 14 to 19. These data show that the composition is immunogenic both at antibody and cellular level in all vaccination groups. More than 85% of subjects mounted a significant antibody response to CagA, VacA and NAP after the third immunisation. The majority of subjects maintained antibody titres above the cut-off limits to all three antigens months after the 3rd dose. The majority of the subjects exhibited a significant antigen-specific cellular proliferative response (particularly CagA and VacA). The composition induces antigen-specific memory, with the antibody response being boostable and significant proliferative responses to at least two of the antigens detectable up to >3 months after the third immunisation

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention.

REFERENCES (the contents of which are hereby incorporated by reference)

1 – Del Giudice *et al.* (2001) *Annu. Rev. Immunol.* 19:523-563.
2 – Chen *et al.* (2000) *Exp. Opin. Ther. Patents* 10:1221-1232.
3 – Telford *et al.* (1997) *Curr. Opin. Immunol.* 9:498-503.
4 – Dundon *et al.* (2001) *Int. J. Med. Microbiol.* 290:647-658.
5 – Telford *et al.* (1994) *TIBTECH* 12:420-426.
6 – Tomb *et al.* (1997) *Nature* 388:539-547.
7 – Alm *et al.* (1999) *Nature* 397:176-180.
8 – Marchetti *et al.* (1995) *Science* 267:1655-1658.
9 – Marchetti *et al.* (1998) *Vaccine* 16:33-37.
10 – Satin *et al.* (2000) *J. Exp. Med.* 191:1467-1476.
11 – Covacci & Rappuoli (2000) *J. Exp. Med.* 19:587-592.
12 – International patent application WO93/18150.
13 – Covacci *et al.* (1993) *Proc. Natl. Acad. Sci. USA* 90: 5791-5795.
14 – Tummuru *et al.* (1994) *Infect. Immun.* 61:1799-1809.
15 – Mukhopadhyay *et al.* (2000) *J. Bacteriol.* 182: 3219-3227.
16 – Telford *et al.* (1994) *J. Exp. Med.* 179:1653-1658.
17 – Ji *et al.* (2000) *Infect. Immun.* 68: 3754-3757.
18 – Manetti *et al.* (1995) *Infect. Immun.* 63:4476-4480.
19 – Manetti *et al.* (1997) *Infect. Immun.* 65:4615-4619.
20 – Evans *et al.* (1995) *Gene* 153:123-127.
21 – International patent applications WO96/01272 & WO96/01273, especially SEQ ID NO:6.
22 – International patent application WO97/25429.
23 – Tonello *et al.* (1999) *Mol. Microbiol.* 34:238-246.
24 – International patent application WO99/53310.
25 – Covacci *et al.* (1999) *Science* 284:1328-1333.
26 – Ross *et al.* (1991) *J Clin Pathol.* 44:876-878.
27 – *Vaccine Design: subunit & adjuvant approach* (1995) Powell & Newman (ISBN: 030644867X)
28 – Rossi *et al.* (1999) *Infect. Immun.* 67:3112-3120.
29 – International patent application WO98/20734.
30 – Sarno *et al.* (2000) *Pediatr. Infect. Dis. J.* 19:839-842.
31 – Savarino *et al.* (1999) *Gut* 45 Suppl. 1:118-122.
32 – Goddard & Logan (1997) *Aliment. Pharmacol. Ther.* 11:641-649.
33 – Vaira *et al.* (2000) *Gastroenterol. Clin. North Am.* 29:917-923.
34 – International patent application WO98/04702.
35 – International patent application WO99/24578.
36 – International patent application WO99/36544.
37 – International patent application WO99/57280.
38 – International patent application WO00/22430.
39 – Tettelin *et al.* (2000) *Science* 287:1809-1815.
40 – International patent application WO96/29412.

41 – Pizza *et al.* (2000) *Science* 287:1816-1820.
42 – International patent application WO01/52885.
43 – Bjune *et al.* (1991) *Lancet* 338(8775):1093-1096.
44 – Fukasawa *et al.* (1999) *Vaccine* 17:2951-2958.
45 – Rosenqvist *et al.* (1998) *Dev. Biol. Stand.* 92:323-333.
46 – Costantino *et al.* (1992) *Vaccine* 10:691-698.
47 – Costantino *et al.* (1999) *Vaccine* 17:1251-1263.
48 – Watson (2000) *Pediatr Infect Dis J* 19:331-332.
49 – Rubin (2000) *Pediatr Clin North Am* 47:269-285, v.
50 – Jedrzejas (2001) *Microbiol Mol Biol Rev* 65:187-207.
51 – Bell (2000) *Pediatr Infect Dis J* 19:1187-1188.
52 – Iwarson (1995) *APMIS* 103:321-326.
53 – Gerlich *et al.* (1990) *Vaccine* 8 Suppl:S63-68 & 79-80.
54 – Hsu *et al.* (1999) *Clin Liver Dis* 3:901-915.
55 – Gustafsson *et al.* (1996) *N. Engl. J. Med.* 334:349-355.
56 – Rappuoli *et al.* (1991) *TIBTECH* 9:232-238.
57 – *Vaccines* (1988) eds. Plotkin & Mortimer. ISBN 0-7216-1946-0.
58 – Del Guidice *et al.* (1998) *Molecular Aspects of Medicine* 19:1-70.
59 – WO02/02606.
60 – Kalman *et al.* (1999) *Nature Genetics* 21:385-389.
61 – Read *et al.* (2000) *Nucleic Acids Res* 28:1397-406.
62 – Shirai *et al.* (2000) *J. Infect. Dis.* 181(Suppl 3):S524-S527.
63 – International patent application WO99/27105.
64 – International patent application WO00/27994.
65 – International patent application WO00/37494.
66 – International patent application WO99/28475.
67 – Ross *et al.* (2001) *Vaccine* 19:4135-4142.
68 – Sutter *et al.* (2000) *Pediatr Clin North Am* 47:287-308.
69 – Zimmerman & Spann (1999) *Am Fam Physician* 59:113-118, 125-126.
70 – Dreesen (1997) *Vaccine* 15 Suppl:S2-6.
71 – *MMWR Morb Mortal Wkly Rep* 1998 Jan 16;47(1):12, 19.
72 – McMichael (2000) *Vaccine* 19 Suppl 1:S101-107.
73 – Schuchat (1999) *Lancet* 353(9146):51-6.
74 – International patent application PCT/GB01/04789.
75 – Dale (1999) *Infect Dis Clin North Am* 13:227-43, viii.
76 – Ferretti *et al.* (2001) *PNAS USA* 98: 4658-4663.
77 – Kuroda *et al.* (2001) *Lancet* 357(9264):1225-1240; see also pages 1218-1219.
78 – Ramsay *et al.* (2001) *Lancet* 357(9251):195-196.
79 – Lindberg (1999) *Vaccine* 17 Suppl 2:S28-36.
80 – Buttery & Moxon (2000) *J R Coll Physicians Lond* 34:163-168.
81 – Ahmad & Chapnick (1999) *Infect Dis Clin North Am* 13:113-133, vii.
82 – Goldblatt (1998) *J. Med. Microbiol.* 47:563-567.

83 – European patent 0 477 508.
84 – US patent 5,306,492.
85 – International patent application WO98/42721.
86 – *Conjugate Vaccines* (eds. Cruse *et al.*) ISBN 3805549326, particularly vol. 10:48-114.
87 – Hermanson (1996) *Bioconjugate Techniques* ISBN: 0123423368 or 012342335X.
88 – European patent application 0372501.
89 – European patent application 0378881.
90 – European patent application 0427347.
91 – International patent application WO93/17712.
92 – International patent application WO98/58668.
93 – European patent application 0471177.
94 – International patent application WO00/56360.
95 – International patent application WO00/61761.
96 – Robinson & Torres (1997) *Seminars in Immunology* 9:271-283.
97 – Donnelly *et al.* (1997) *Annu Rev Immunol* 15:617-648.
98 – Scott-Taylor & Dalgleish (2000) *Expert Opin Investig Drugs* 9:471-480.
99 – Apostolopoulos & Plebanski (2000) *Curr Opin Mol Ther* 2:441-447.
100 – Ilan (1999) *Curr Opin Mol Ther* 1:116-120.
101 – Dubensky *et al.* (2000) *Mol Med* 6:723-732.
102 – Robinson & Pertmer (2000) *Adv Virus Res* 55:1-74.
103 – Donnelly *et al.* (2000) *Am J Respir Crit Care Med* 162(4 Pt 2):S190-193.
104 – Davis (1999) *Mt. Sinai J. Med.* 66:84-90.
105 – WO98/54171
106 – WO99/00380
107 – WO99/28322.
108 – US patent 6265415.
109 – US patent 6160119.
110 – US patent 5925667.
111 – US patent 5891890.
112 – US patent 6001880.
113 – US patent 6077830.
114 – Chen *et al.* (2000) *Exp. Opin. Ther. Patents* 10:1221-1232.
115 – Ermak *et al.* (1998) *J. Exp. Med.* 188:2277-2288.
116 – Rossi *et al.* (2000) *Infect. Immun.* 68:4769-4772.
117 – Ghiara *et al.* (1997) *Infect. Immun.* 65:4996-5002.
118 – Percy *Pathology of Laboratory Rodents and Rabbits*. Iowa State University Press; 1993.
119 – Goto *et al.* (1982) *Microbiol. Immunol.* 26(12):1121-1132.
120 – Goto *et al.* (1997) *Vaccine* 15:1364-1371.

CLAIMS

1. A composition in unit dosage form comprising (a) *H.pylori* CagA, VacA and NAP proteins; (b) an aluminium salt adjuvant: and (c) a buffer solution, wherein CagA, VacA and NAP are each present at a concentration of between 10 μg/dose and 50 μg/dose.

2. A composition comprising: (a) *H.pylori* CagA, VacA and NAP proteins; (b) an aluminium salt adjuvant; (c) a buffer solution: and (d) urea.

3. The composition of claim 1, wherein CagA, VacA and NAP are each present at a concentration of 10 μg/dose.

4. The composition of claim 2, wherein CagA, VacA and NAP are each present at a concentration of 20 μg/ml.

5. The composition of claim 1, wherein CagA, VacA and NAP are each present at a concentration of 25 μg/dose.

6. The composition of claim 2, wherein CagA, VacA and NAP are each present at a concentration of 50 μg/ml.

7. The composition of any preceding claim, wherein the alum salt is aluminium hydroxide.

8. The composition of claim 7, wherein the aluminium hydroxide has a concentration of 1 mg/ml.

9. The composition of any preceding claim, wherein the buffer solution is a phosphate buffer.

10. The composition of any preceding claim, buffered to a pH of between 6 and 8.

11. The composition of any preceding claim, wherein the composition is isotonic.

12. The composition of any preceding claim, wherein the composition is sterile.

13. The composition of any preceding claim, adapted for intramuscular administration.

14. The composition of claim 13, adapted for administration as an injectable.

15. The composition of any one of claims 2 to 14, wherein urea is present in an amount sufficient to ensure that VacA remains soluble.

16. The composition of any preceding claim, further comprising an antigen selected from the group consisting of:
    - a protein antigen from *N.meningitidis*;
    - an outer-membrane vesicle (OMV) preparation from *N.meningitidis*;
    - a saccharide antigen from *N.meningitidis*;
    - a saccharide antigen from *Streptococcus pneumoniae*;

– an antigen from hepatitis A, B and/or C virus;
– an antigen from *Bordetella pertussis*;
– a diphtheria antigen;
– a tetanus antigen;
– a protein antigen from *Helicobacter pylori*;
– a saccharide antigen from *Haemophilus influenzae*;
– an antigen from *N.gonorrhoeae*;
– an antigen from *Chlamydia pneumoniae*;
– an antigen from *Chlamydia trachomatis*;
– an antigen from *Porphyromonas gingivalis*;
– polio antigen(s);
– rabies antigen(s);
– measles, mumps and/or rubella antigens;
– influenza antigen(s);
– an antigen from *Moraxella catarrhalis*;
– an antigen from *Streptococcus agalactiae*;
– an antigen from *Streptococcus pyogenes*; and
– an antigen from *Staphylococcus aureus*.

17. The composition of any preceding claim, being an immunogenic composition.

18. The composition of any preceding claim, wherein said composition is a vaccine composition.

19. The composition of any preceding claim, further comprising an antisecretory agent and/or an antibiotic effective against *Helicobacter pylori*.

20. The composition of claim 19, wherein the antisecretory agent is a proton pump inhibitor, a H2 receptor antagonist, a bismuth salt or a prostaglandin analog.

21. A kit comprising a syringe, a needle, and the composition of any preceding claim.

22. The kit of claim 21 wherein the composition is within the syringe.

23. The kit of claim 21 or claim 22, further comprising an antisecretory agent and/or an antibiotic effective against *Helicobacter pylori*.

24. The kit of claim 23, wherein the antisecretory agent is a proton pump inhibitor, a H2 receptor antagonist, a bismuth salt or a prostaglandin analog.

25. A process for producing the composition of any one of claims 1 to 20, comprising the step of admixing *H.pylori* CagA, VacA and NAP proteins, an aluminium salt, and a buffer solution.

26. A method for raising an immune response in a mammal, comprising the step of administering an effective amount of the composition of any one of claims 1 to 18.

27. The method of claim 24, wherein the mammal is a human.

28. The method of claim 25, wherein the human is a child or an adult.

29. The method of any one of claims 26 to 28, wherein the composition of any one of claims 1 to 18 is administered in conjunction with an antisecretory agent and/or an antibiotic effective against *Helicobacter pylori*.

30. The composition of any one of claims 1 to 20, for use as a medicament.

31. The use of the composition of any one of claims 1 to 20 in the manufacture of a medicament for raising an immune response in a mammal against CagA, VacA and NAP.

32. The use of (a) the composition of any one of claims 1 to 18 and (b) an antisecretory agent and/or an antibiotic effective against *Helicobacter pylori*, in the manufacture of a medicament for raising an immune response in a mammal against CagA, VacA and NAP.

33. The composition of claim 30, or the use of claim 31 or claim 32, wherein the medicament is for the prevention and/or treatment of an infection and/or disease caused by *Helicobacter pylori* at any age.

34. A process for monitoring the efficacy of a composition of any one of claims 1 to 20 or the method of any one of claims 26 to 29, wherein one or more of the following tests is performed on a patient to whom the composition has been administered: urease breath test, stool antigen shedding, and/or immunological (*e.g.* serological) analysis.

35. The process of claim 34, wherein the process monitors prophylactic efficacy.

36. The process of claim 34, wherein the process monitors therapeutic efficacy.

37. The use of urease breath testing, stool antigen testing, and/or immunological (*e.g.* serological) analysis as correlate(s) of protection against *H.pylori* infection.

FIGURE 1

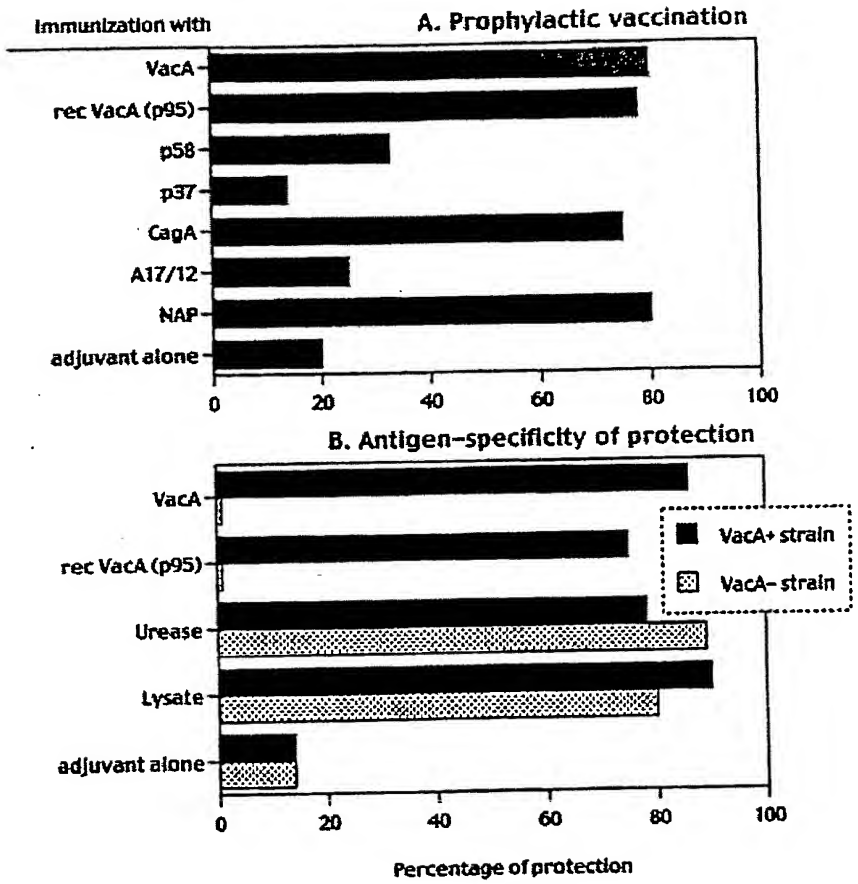

Immunization with
A. Prophylactic vaccination
VacA
rec VacA (p95)
p58
p37
CagA
A17/12
NAP
adjuvant alone
0
20
40
60
80
100
B. Antigen-specificity of protection
VacA
rec VacA (p95)
Urease
Lysate
adjuvant alone
VacA+ strain
VacA- strain
0
20
40
60
80
100
Percentage of protection

FIGURE 2A

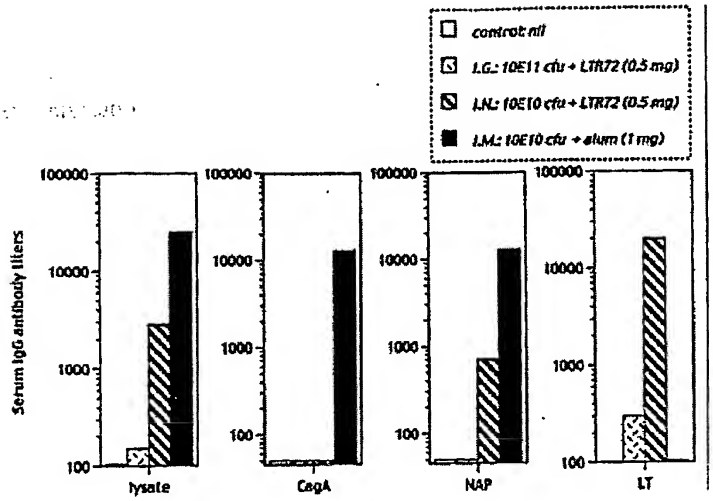


FIGURE 2B

Immunization	Dog #	Protection
nil	1	-
	2	-
	3	-
Intragastric	4	-
	5	-
	6	-
	7	+
Intramuscular	8	+
	9	+
	10	+
Intranasal	11	+
	12	-
	13	-

FIGURE 3

FIGURE 3A

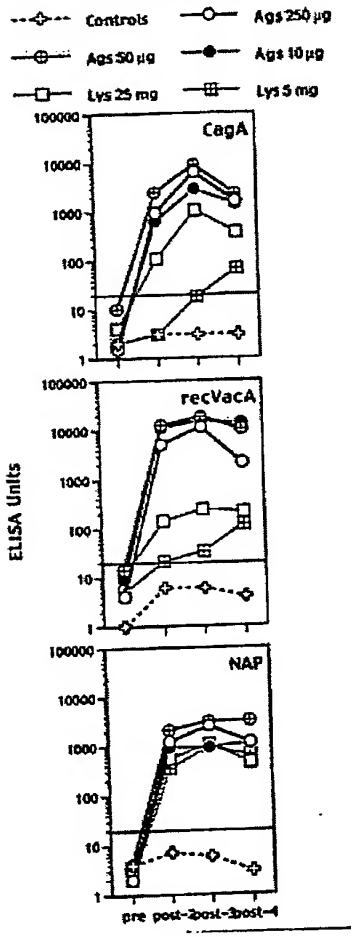


FIGURE 3B

Group	Dog #	Protection
Control	1	–
	2	–
	3	–
	4	–
VacA/CagA/NAP 250 mg each	5	+
	6	+
	7	+
	8	–
VacA/CagA/NAP 50 mg each	9	+
	10	+
	11	+
	12	+
VacA/CagA/NAP 10 mg each	13	+
	14	+
	15	+
	16	+
whole-cell lysate 25 mg	17	–
	18	+
	19	+
	20	+
whole-cell lysate 5 mg	21	+
	22	+
	23	–
	24	+

FIGURE 4

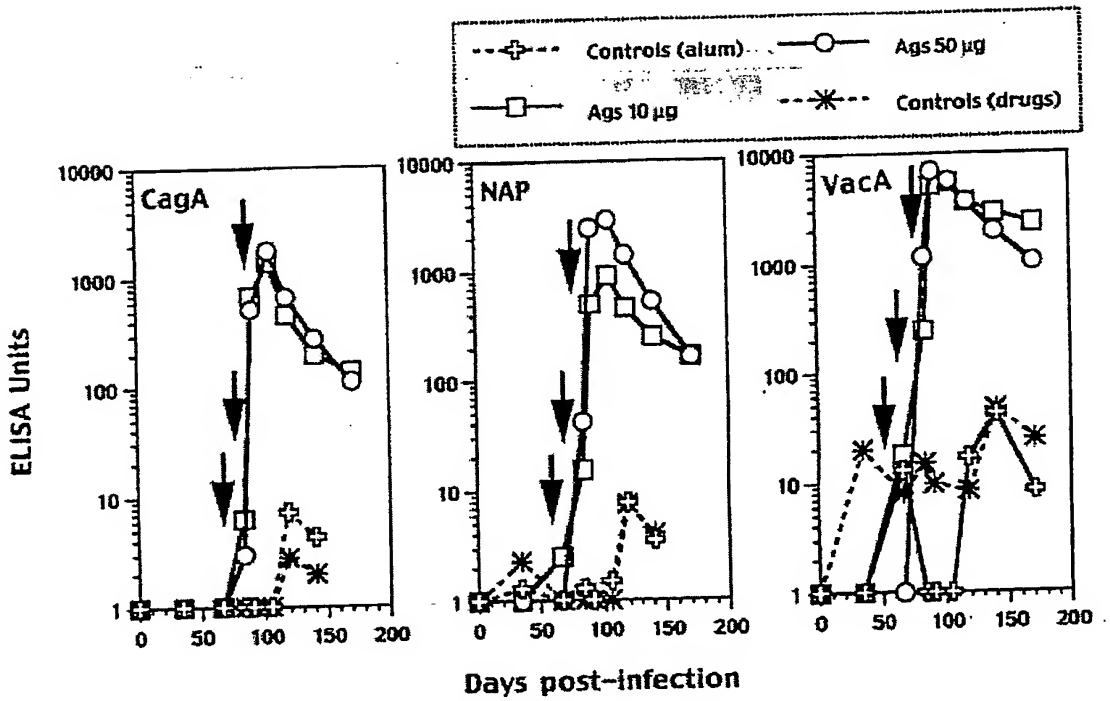

Controls (alum)
Ags 50 µg
Ags 10 µg
Controls (drugs)
CagA
NAP
VacA
ELISA Units
Days post-infection
10000
1000
100
10
1
0
50
100
150
200

FIGURE 5

		pre-vaccination				week 7 post-vaccination				week 11 post-vaccination				week 17 post-vaccination				week 27 post-vaccination			
group	dog n.	antrum inflammation	antrum follicles	urease	immunohistochemistry	antrum inflammation	antrum follicles	urease	immunohistochemistry	antrum inflammation	antrum follicles	urease	immunohistochemistry	antrum inflammation	antrum follicles	urease	immunohistochemistry	antrum inflammation	antrum follicles	urease	immunohistochemistry
1 alum	10	3	3	+	+	3	3	+	+	3	3	+	+	3	3	+	+	2	1	+	+
	11	1	0	+	+	3	0	+	+	2	0	+	+	2	0	+	+	2	1	+	+
	14	0	0	+	-	2	0	+	+	3	3	+	+	3	3	+	+	1	1	+	+
	8	3	3	+	+	3	0	+	+	2	0	+	+	0	0	+	+	2	1	+	+
2 HP3 50 µg	3	0	0	+	-	1	0	+	+	2	1	+	-	0	0	-	-	2	0	+	-
	1	2	2	+	+	1	0	+	+	0	0	+	-	0	0	-	-	1	1	+	+
	6	3	3	+	+	2	1	+	-	2	2	+	+	2	0	+	+	0	0	+	+
	7	2	0	+	+	0	0	+	-	0	0	+	-	0	0	+	+	2	2	+	-
3 HP3 10 µg	2	3	3	+	+	3	3	+	+	1	0	+	+	0	0	-	-	0	0	+	+
	12	2	1	+	+	1	0	+	-	0	0	+	-	0	0	+	+	2	2	+	-
	15	3	3	+	+	1	1	+	+	0	0	+	+	0	0	+	+	1	0	+	-
	9	3	3	+	+	0	0	+	-	2	2	+	-	1	0	-	-	2	0	+	-
4 PPI + antib.	4	3	2	+	+	1	0	-	+	0	0	-	-	0	0	-	-	3	0	+	-
	5	2	0	+	+	3	3	-	-	1	0	-	-	0	0	-	-	1	0	+	+
	13	3	3	+	+	3	3	-	-	0	0	+	+	3	3	+	+	1	0	+	+
	16	3	3	+	+	0	0	+	+	2	2	+	+	1	0	+	+	1	0	+	+

5/11

FIGURE 6

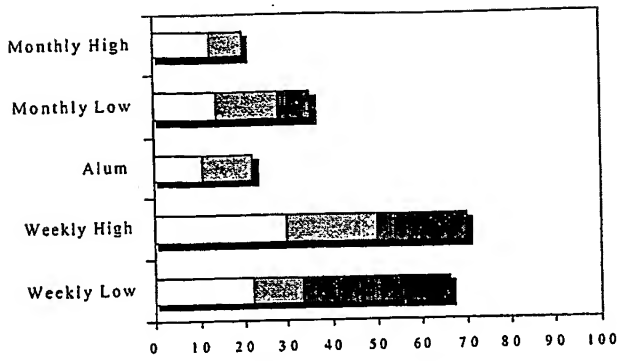


FIGURE 7

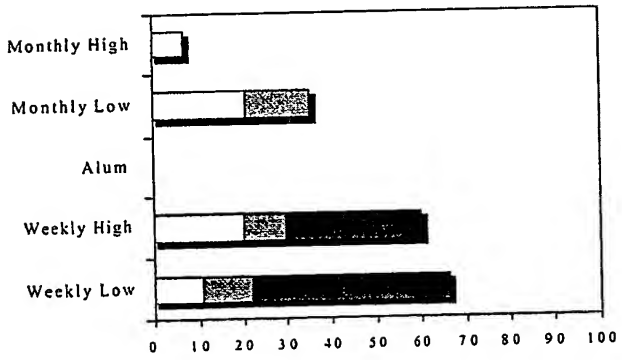


FIGURE 8

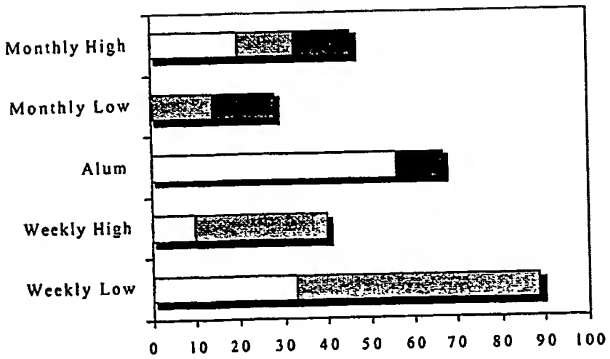


FIGURE 9

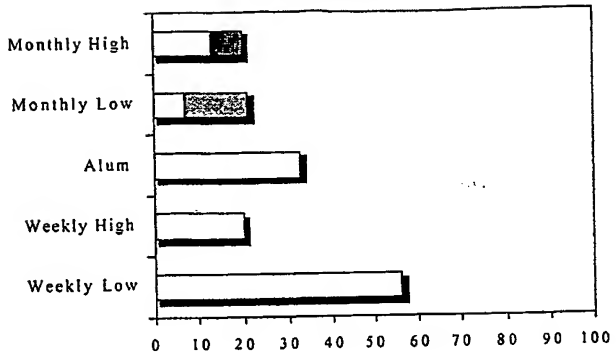


FIGURE 10

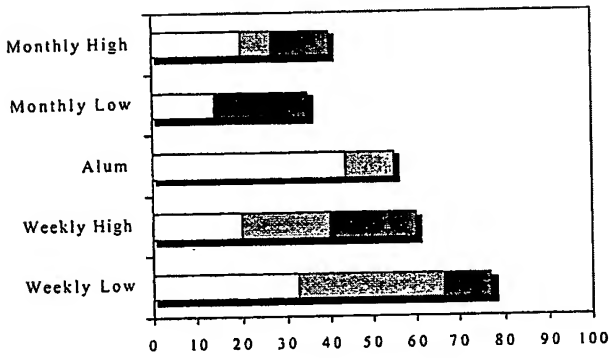


FIGURE 11

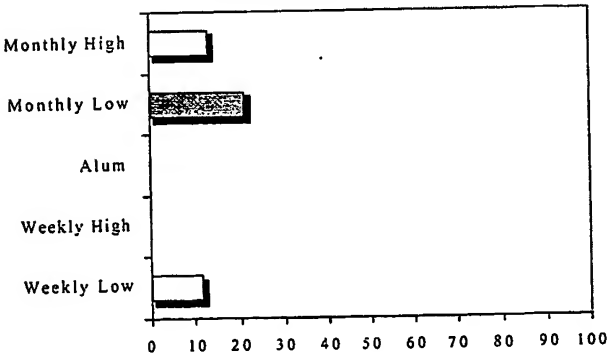


FIGURE 12

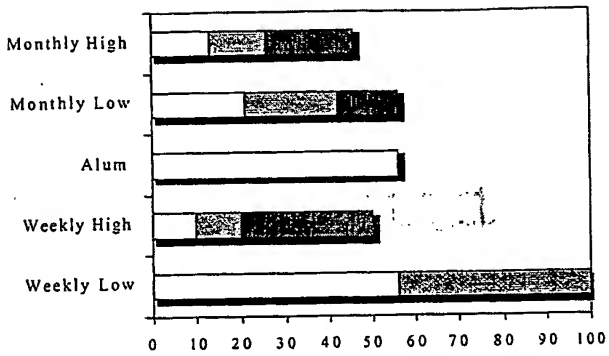


FIGURE 13

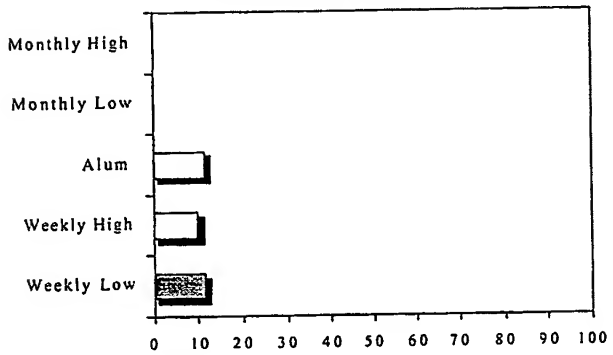


FIGURE 14

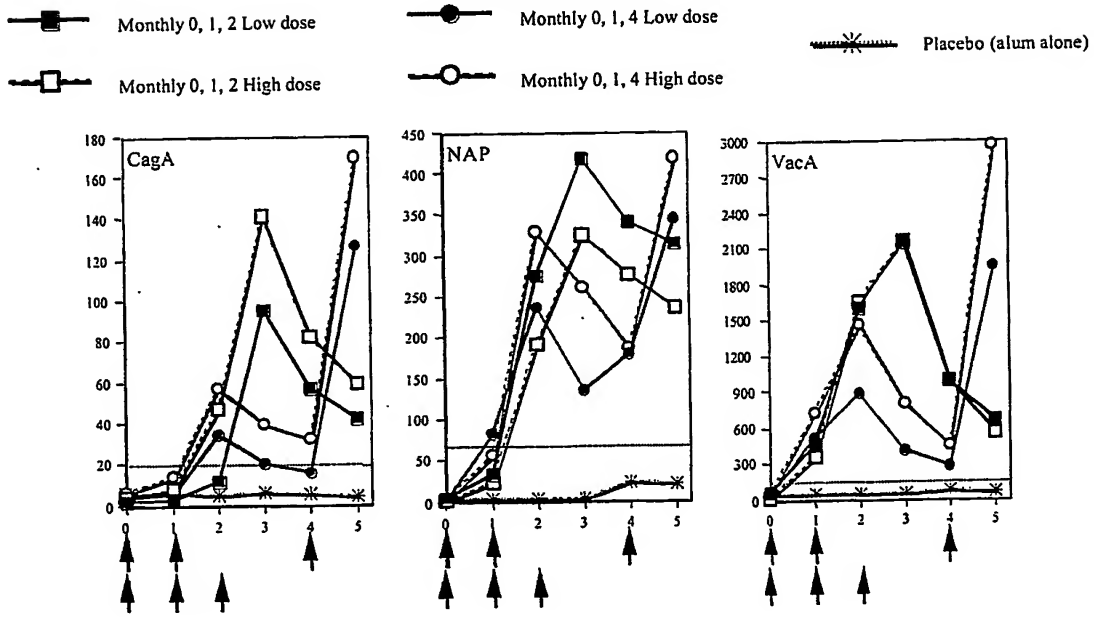


FIGURE 15

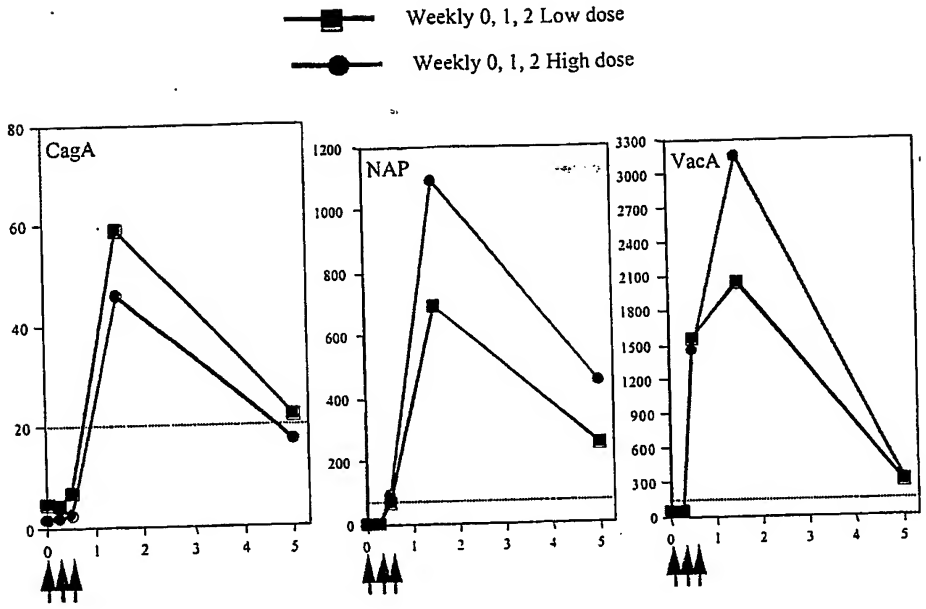


FIGURE 16

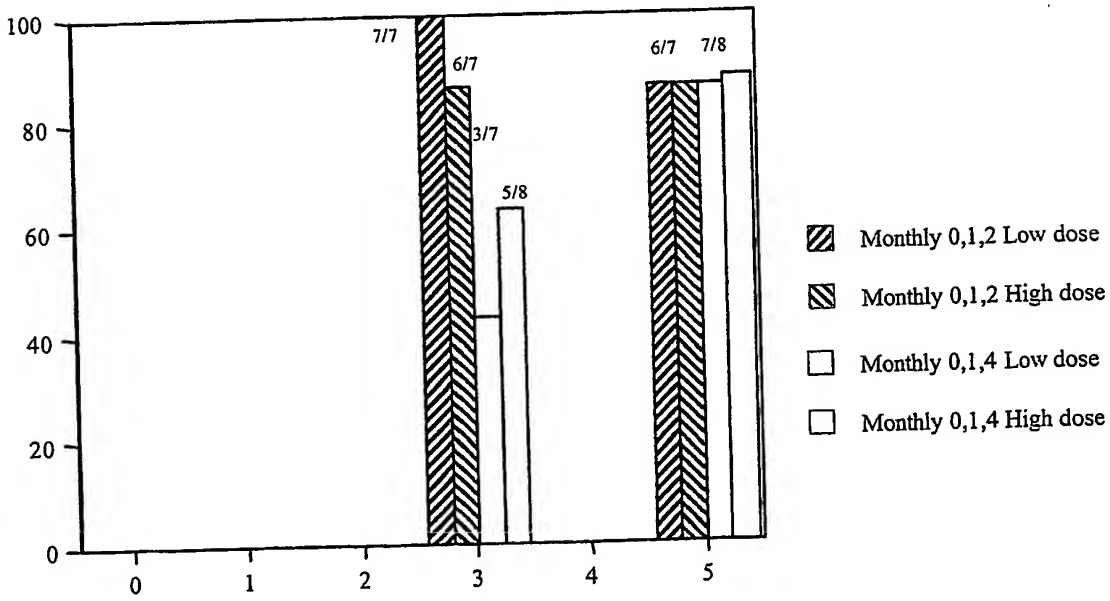


FIGURE 17

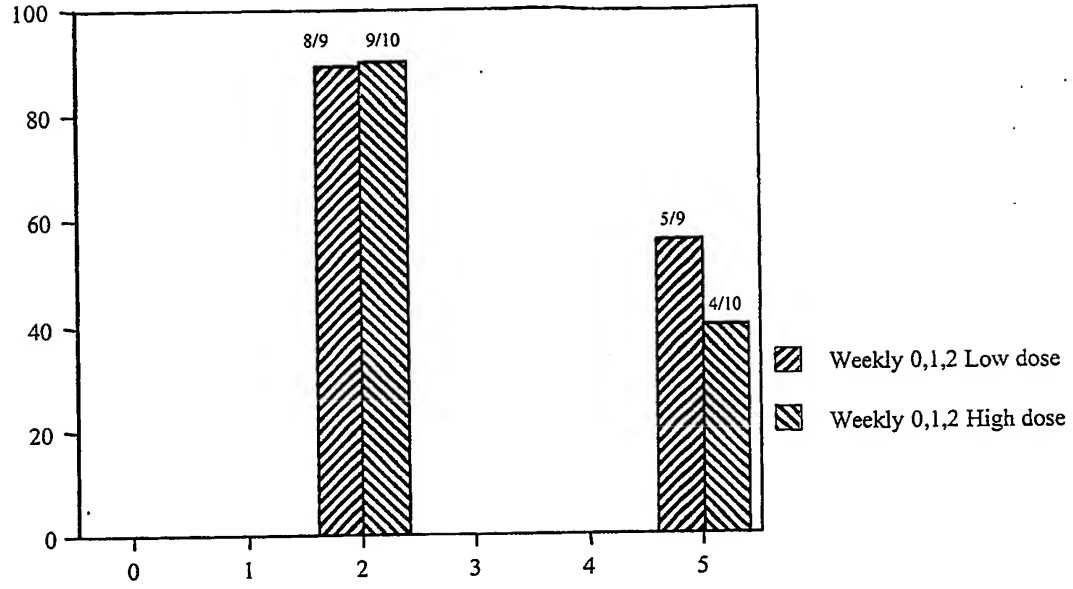


FIGURE 18

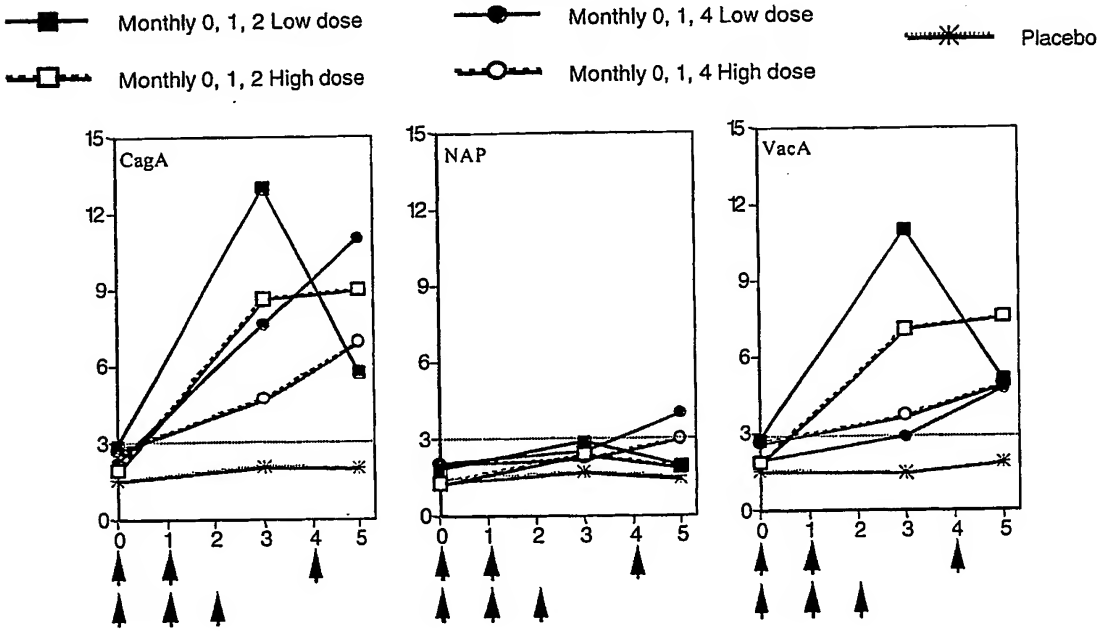
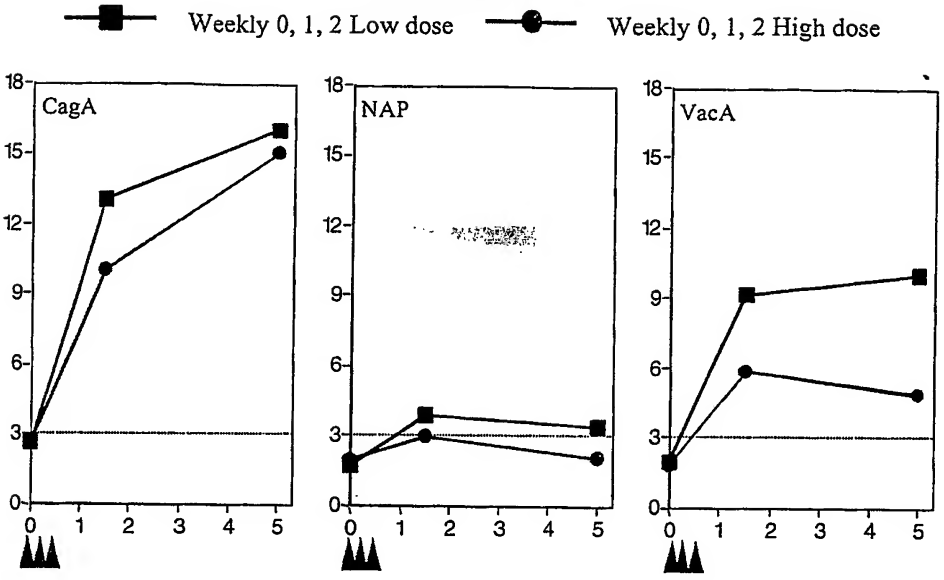


FIGURE 19


Weekly 0, 1, 2 Low dose
Weekly 0, 1, 2 High dose
CagA
NAP
VacA
18
15
12
9
6
3
0
0 1 2 3 4 5